Part I Overview Information

Department of Health and Human Services

Participating Organizations
National Institutes of Health (NIH), (http://www.nih.gov)

Components of Participating Organizations
National Institute of Allergy and Infectious Diseases (NIAID), (http://www.niaid.nih.gov)
National Institute of Neurological Disorders and Stroke (NINDS), (http://www.ninds.nih.gov)
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), (http://www.niddk.nih.gov)
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), (http://www.niams.nih.gov)

Title: Hyperaccelerated Award/Mechanisms in Immunomodulation Trials

Announcement Type
This is a renewal with modifications of RFA-AI-04-001 which was released on November 10, 2003 (http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-04-001.html).

Request For Applications (RFA) Number: **RFA-AI-05-028**

Catalog of Federal Domestic Assistance Number(s)
93.855, 93.847, 93.853, 93.866

Key Dates
Release Date: June 28, 2005
Letters of Intent Receipt Date(s): At least one month prior to application receipt date
Application Receipt Dates(s): Applications will be accepted MONTHLY on the ninth of each month beginning on July 9, 2005 and ending June 9, 2006
Peer Review Date(s): Approximately eight weeks after submission
Council Review Date(s): Special Electronic Council
Earliest Anticipated Start Date: Thirteen weeks after receipt date
Additional Information To Be Available Date (Url Activation Date):
http://www.niaid.nih.gov/ncn/budget/QA/rfa-05-028.htm
Expiration Date: June 10, 2006

Due Dates for E.O. 12372
Not Applicable

Additional Overview Content

Executive Summary

- This RFA invites R01 applications for mechanistic studies in clinical trials of: immunomodulatory interventions for immune system mediated diseases, including, but not limited to: asthma and allergic diseases; graft failure in solid organ, cell, tissue and stem cell transplantation; and chronic inflammatory, autoimmune, and immunodeficiency diseases;

preventative and therapeutic, vaccines for non-HIV/AIDS infectious diseases, including NIAID Category A, B, and C agents of bioterrorism and emerging/re-emerging infectious diseases.

- This Request for Applications (RFA) is a renewal with modifications of RFA-AI-04-001 (http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-04-001.html).
- In order to review and confer awards to grant applications received in response to this RFA in a timely fashion, without delay of the parent clinical trial, applications submitted in response to the RFA will be subject to a hyperaccelerated review/award process. Highly meritorious applications selected for funding under this RFA may receive their awards as early as thirteen weeks after the application receipt date. Holidays and other circumstances may alter this schedule slightly.
- The National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Neurological Disorders and Stroke (NINDS), and National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health (NIH) intend to commit $1.6 million in Fiscal Year 2006 to fund four to five applications. The total requested project period for an application submitted in response to this RFA may not exceed four years.
- Eligible organizations include for-profit or non-profit organizations, public or private institutions (e.g., universities, colleges, hospitals), units of state and local governments, and eligible agencies of the Federal government. Both domestic and foreign institutions are eligible to apply.
- Eligible principal investigators include any individual with the skills, knowledge, and resources necessary to carry out the proposed research. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are encouraged to apply for NIH programs.
- Only under extraordinary circumstances and with the approval of the participating ICs would an applicant be allowed to submit more than one application per fiscal year (October 1 – September 30) as a Principal Investigator. Amended applications will ONLY be accepted for Hyperaccelerated Review/Award if invited by the sponsoring NIH Institutes.
- See Section IV.1 for application materials.
- Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 9/2004); The PHS 398 document is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: Grantsinfo@nih.gov.
- Telecommunications for the hearing impaired is available at: TTY 301-451-0088.

Table of Contents

Part II - Full Text of Announcement

Section I. Funding Opportunity Description

1. Research Objectives

In December 1996, NIAID convened a workshop at which leading basic and clinical immunologists discussed the role the NIH should play in current and projected clinical trials for various immune mediated diseases. It was considered likely that clinical trials of many new immunologic interventions would be supported by the pharmaceutical/biotechnology industry. However, gaps in both knowledge and in research effort were identified which represent opportunities for the NIH to contribute to progress in this area.

There was agreement that the mechanisms underlying immunologic interventions are poorly understood even in cases where efficacy has been shown (e.g., allergen immunotherapy, treatment of multiple sclerosis with interferons or Copolymer-I, and in other immunomodulatory regimens under development). In addition, clinical trials supported by industry and other sources including NIH often do not include studies of underlying mechanisms. There was consensus that high priority should be given to the utilization of patient samples from interventional clinical trials in immunologic diseases for studies of the basic underlying mechanisms of therapeutic effect, immunologic function, and disease pathogenesis.

There was also agreement that the usual time required for grant review and funding is often incompatible with the time-line of a clinical trial. Specifically, when a clinical protocol is finalized (which is required for applications submitted under this RFA), investigators are often ready to begin as soon as Institutional Review Board approval is obtained. NIAID was encouraged to develop a means of responding rapidly to opportunities to study underlying mechanisms in order to facilitate collaborations with industry-supported clinical trials.

These recommendations were strongly supported by a large number of investigators who participated in NIAID focus groups in the winter/spring of 1997. A pilot program was instituted in 1998 (RFA AI-98-006) to implement these recommendations and exploit the research opportunities identified. Based on the successful implementation of these initiatives and the ensuing RFAs (RFA-AI-00-005, RFA-AI-01-001, RFA-AI-02-003, and RFA-AI-04-001) the current RFA is being issued.

The objective of this RFA is to support mechanistic research studies in clinical trials of immunomodulatory interventions for: (1) immune system mediated diseases, including: asthma and allergic diseases; graft failure in solid organ, cell and tissue transplantation; graft versus host disease in hematopoietic stem cell transplantation; and chronic inflammatory, autoimmune, and immunodeficiency diseases; and (2) vaccines for the prevention and treatment of non-HIV/AIDS infectious diseases, including NIAID Category A, B and C agents of bioterrorism and emerging/re-emerging infectious diseases (see list of agents at http://www.niaid.nih.gov/biodefense/bandc_priority.htm.)

Specifically, the goal of this RFA is the inclusion of patients and utilization of patient samples from such clinical trials for the evaluation of immunologic and other relevant parameters in order to study and define the underlying immunological mechanisms of the intervention or vaccine, the mechanisms of disease pathogenesis, biomarkers of disease activity and therapeutic effect, and mechanisms of human immunologic function. Such studies are not part of the parent clinical trial, and are commonly referred to as substudies or ancillary studies. The parent clinical trial must have independent financial support and will NOT receive support under this RFA. Proposed mechanistic studies associated with clinical trials supported by industry are particularly encouraged but clinical trials supported by any source, public or private, are eligible. Clinical trials of any phase (i.e., Phases I-IV) are eligible. Examples of relevant research include, but are not limited to, the following:

- Quantitation of disease-related, autoreactive or alloreactive lymphocytes using methods such as MHC/peptide tetramers, chimeric antibodies, or very early activation antigens.
- Analysis of autoreactive or alloreactive cells by PCR for expression of genes implicated in immunity or inflammation, or by flow cytometry for cell surface markers that identify functions (e.g., cytokine receptors that distinguish Th1 from Th2 or chemokine receptors or integrins that indicate preferential patterns of homing).
- Assessment of reagents that can identify populations of regulatory T cells which appear to be altered in autoimmune disease.
- Identification and evaluation of cytokine and cytokine receptor polymorphisms and analysis for genetic linkage to disease.
- Immune mechanisms of vaccines. Studies to define the underlying mechanisms of protection induced by vaccines against infectious diseases, including investigation of the specificity and kinetics of cellular and antibody responses, Th1/Th2 and cytotoxic T cell characterization, and immune memory.
- Use of high throughput technologies (e.g., chip technology) to identify and evaluate genes activated in disease sites.
- Identification of useful biomarkers that correlate with disease activity and/or response to intervention or vaccine.
- Comparison of immune parameters between peripheral blood samples and biopsy samples from sites of disease, i.e., do peripheral blood samples provide useful information?
- Assessment of potential causative environmental agents through the use of molecular evidence (e.g., using PCR probes).

- The molecular and cellular mechanisms by which lymphocytes, macrophages, neutrophils, antibodies, cytokines and complement contribute to successful immunotherapy for chronic inflammatory diseases.

The areas outlined above are examples and are not intended to be all-inclusive.

Clinical trials responsive to this RFA must be interventional trials of immunomodulatory agents for immune-mediated diseases, or vaccines for non-HIV/AIDS infectious diseases.

Clinical trials of drug treatments (e.g., antibiotics or antiviral drugs) for infectious diseases (e.g., Lyme Disease), and vaccines and drug/immunomodulatory treatment for HIV/AIDS are NOT eligible for support under this RFA.

Applicants are strongly encouraged to contact program staff listed under WHERE TO SEND INQUIRIES well in advance of the anticipated application submission date to allow staff to assess responsiveness to this RFA and provide appropriate guidance as needed.

See Section VIII, Other Information - Required Federal Citations, for policies related to this announcement.

Section II. Award Information

1. Mechanism(s) of Support

This funding opportunity will use the R01 award mechanism(s). The total requested project period for an application submitted in response to this RFA may not exceed four years. Future unsolicited, competing-continuation applications based on this project will compete with all investigator-initiated applications and will be reviewed according to the customary peer review procedures.

As an applicant, you will be solely responsible for planning, directing, and executing the proposed project.

This funding opportunity uses just-in-time concepts. It also uses the modular budget format described in the PHS 398 application instructions (see http://grants.nih.gov/grants/funding/modular/modular.htm).

2. Funds Available

The participating IC(s) NIAID, NINDS, NIDDK, and NIAMS , intend to commit approximately 1.6 million dollars in FY 2006 to fund four to five new grants in response to this RFA. An applicant may request a project period of up to four years and a budget for direct costs up to 250,000 dollars per year.

Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary. In previous years of this program, the amount of funding has ranged from 75,000 to 250,000 dollars annual direct costs. Although the financial plans of the IC(s) provide support for this program, awards pursuant to this funding opportunity are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications.

Facilities and administrative costs requested by consortium participants are not included in the direct cost limitation, see NOT-OD-05-004.

Section III. Eligibility Information

1. Eligible Applicants

1.A. Eligible Institutions

You may submit (an) application(s) if your organization has any of the following characteristics:

- Non-profit organizations
- Public or private institutions, such as universities, colleges, hospitals, and laboratories
- For-profit organizations
- Units of State government
- Units of local government
- Eligible agencies of the Federal government
- Foreign Institutions
- Domestic Institutions

1.B. Eligible Individuals

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

2. Cost Sharing or Matching

This program does not require cost sharing, matching or participation.

3. Other-Special Eligibility Criteria

Amended applications will ONLY be accepted for Hyperaccelerated Review/Award if invited by the sponsoring NIH Institutes. , Applicants with minor or easily corrected problems may be invited to submit either a fully amended application, or an abbreviated amendment (five page limit and one time only) which directly addresses the questions and concerns raised in the initial review.

Section IV. Application and Submission Information

1. Address to Request Application Information

The PHS 398 application instructions are available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. Applicants must use the currently approved version of the PHS 398. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

Telecommunications for the hearing impaired: TTY 301-451-0088.

2. Content and Form of Application Submission

Applications must be prepared using the most current PHS 398 research grant application instructions and forms. Applications must have a D&B Data Universal Numbering System (DUNS) number as the universal identifier when applying for Federal grants or cooperative agreements. The D&B number can

be obtained by calling (866) 705-5711 or through the web site at http://www.dnb.com/us/. The D&B number should be entered on line 11 of the face page of the PHS 398 form.

The title and number of this funding opportunity must be typed on line 2 of the face page of the application form and the YES box must be checked.

Instructions for the most current PHS 398 must be followed, with the exception that Items a - d of the Research Plan (Specific Aims, Background and Significance, Preliminary Studies, and Research Design and Methods) may not exceed a total of 15 pages. See Section IV.6 for details of specific requirements for applications in response to this RFA.

Foreign Organizations

Several special provisions apply to applications submitted by foreign organizations:

- Charge back of customs and import fees is not allowed.
- Format: every effort should be made to comply with the format specifications, which are based upon a standard US paper size of 8.5" x 11."
- Funds for up to 8% administrative costs (excluding equipment) can now be requested (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-028.html).
- Organizations must comply with federal/NIH policies on human subjects, animals, and biohazards.
- Organizations must comply with federal/NIH biosafety and biosecurity regulations. See Section VI.2. Administrative Requirements, "Cooperative Agreement Terms and Conditions of Award".

Proposed research should provide a unique research opportunity not available in the U.S.

3. Submission Dates and Times

Applications must be received on or before the receipt date described below (Section IV.3.A).

3.A. Receipt, Review and Anticipated Start Dates

Letter of Intent Receipt Date: At least one month prior to application receipt date
Application Receipt Date(s): Monthly, beginning July 9, 2005 and ending on June 9, 2006
Peer Review Date: Approximately eight weeks after receipt date
Council Review Date: Special Electronic Council
Earliest Anticipated Start Date: Thirteen weeks after receipt of application

3.A.1. Letter of Intent

Prospective applicants are asked to submit a letter of intent that includes the following information:

- Descriptive title of proposed research
- Name, address, and telephone number of the Principal Investigator
- Names of other key personnel
- Participating institutions
- Number and title of this funding opportunity

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review.

The letter of intent is to be sent by the date listed at the beginning of this document.

The letter of intent should be sent to:

Mercy Prabhudas, Ph.D.
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases
Room 3256, MSC-7616
6700B Rockledge Drive
Bethesda, MD 20892-7616 (U.S. Postal Service Express or regular mail)
Bethesda, MD 20892 (for express/courier service; non-USPS service)
Telephone: 301-451-2615
FAX: 301-402-2638
E-mail: mprabhudas@niaid.nih.gov

3.B. Sending an Application to the NIH

Applications must be prepared using the research grant applications found in the PHS 398 instructions for preparing a research grant application. Submit a signed, typewritten original of the application, including the checklist, and three signed photocopies in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710 (U.S. Postal Service Express or regular mail)
Bethesda, MD 20817 (for express/courier service; non-USPS service)

Personal deliveries of applications are no longer permitted (see http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-040.html).

At the time of submission, two additional copies of the application and all copies of the appendix material must be sent to:

Mercy Prabhudas, Ph.D.
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases
Room 3256, MSC-7616
6700B Rockledge Drive
Bethesda, MD 20892-7616 (U.S. Postal Service Express or regular mail)
Bethesda, MD 20892 (for express/courier service; non-USPS service)
Telephone: 301-451-2615
FAX: 301-402-2638
E-mail: mprabhudas@niaid.nih.gov

Applications must be received by the ninth of each month. If the ninth of the month falls on a weekend day or Federal Holiday, then the receipt date is advanced to the next business day. The application must not arrive more than two days prior to the receipt date. Applications which are received after the ninth will automatically be processed the following month.

Applications not received as a single package on the receipt date or not conforming to the instructions in the most current PHS 398 as modified by the special instructions below (Section IV.6) for the purposes of this RFA, will be judged non-responsive and will be returned to the applicant.

Using the RFA Label: The RFA label available in the PHS 398 application instructions must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review

committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at: http://grants.nih.gov/grants/funding/phs398/labels.pdf.

3.C. Application Processing

Applications must be **received on or before the application receipt date(s)** described above (Section IV.3.A.). Upon receipt, applications will be evaluated for completeness by the CSR and responsiveness by the sponsoring NIH Institutes. Incomplete and non-responsive applications will not be reviewed.

Amended applications will ONLY be accepted for Hyperaccelerated Review/Award if invited by the sponsoring NIH Institutes. , Applicants with minor or easily corrected problems may be invited to submit either a fully amended application, or an abbreviated amendment (five page limit and one time only) which directly addresses the questions and concerns raised in the initial review.

The NIH will not accept any application in response to this funding opportunity that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within eight (8) weeks.

4. Intergovernmental Review

This initiative is not subject to intergovernmental review.

5. Funding Restrictions

All NIH awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm. When clinical studies are a component of the proposed research, awards will be subject to the NIAID Clinical Terms of Award (information available at http://www.niaid.nih.gov/ncn/sop/ctoa.htm).

Pre-Award Costs are allowable. A grantee may, at its own risk and without NIH prior approval, incur obligations and expenditures to cover costs up to 90 days before the beginning date of the initial budget period of a new or competing continuation award if such costs: are necessary to conduct the project, and would be allowable under the grant, if awarded, without NIH prior approval. If specific expenditures would otherwise require prior approval, the grantee must obtain NIH approval before incurring the cost. NIH prior approval is required for any costs to be incurred more than 90 days before the beginning date of the initial budget period of a new or competing continuation award.

The incurrence of pre-award costs in anticipation of a competing or non-competing award imposes no obligation on NIH either to make the award or to increase the amount of the approved budget if an award is made for less than the amount anticipated and is inadequate to cover the pre-award costs incurred. NIH expects the grantee to be fully aware that pre-award costs result in borrowing against future support and that such borrowing must not impair the grantee's ability to accomplish the project objectives in the approved time frame or in any way adversely affect the conduct of the project. See NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part6.htm.

6. Other Submission Requirements

1. Application:

The research plan is limited to 15 pages. In addition to the specific aims, background and significance, preliminary studies, and research design and methods (Sections A to D), the research plan must include a justification for why the proposed studies require the use of patients in the parent clinical trial as opposed to using patients with the same disease state but not in a trial. The manner in which immunological parameters will be related to the clinical outcomes in the main study should also be discussed.

Methods of data analysis and power calculations must be included, as well as a justification for the required sample size. A restatement of the sample size calculations from the parent clinical trial is insufficient. If appropriate to your application, discuss whether it is necessary to perform the mechanistic studies on all patients enrolled in the parent trial or whether a sub-sample would be sufficient. The plan must also include a discussion of the statistical procedures that will be used to analyze the data. It is strongly recommended that a statistician be part of the research team and active in preparation of the proposal.

2. Appendix:

Appendix should contain the following clearly labeled materials:

- parent clinical trial protocol
- investigator's brochure, if applicable, for the parent clinical trial
- consent forms for both the parent clinical trial and the mechanistic studies, if different
- Institutional Review Board (IRB) approval or the parent clinical trial and ancillary studies, if completed (Note: IRB approval is not required at the time of submission of the application)
- written agreement for conduct of the mechanistic studies from parent clinical trial sponsors, IND holders, and PI of the parent clinical trial

The protocol and the investigators' brochure for the parent clinical trial should be included with the application as part of the human subjects' section. Inclusion of the complete clinical protocol within the PHS 398 grant application is intended to simplify the application process by eliminating the need to duplicate protocol details in the Research Plan section. NIH will treat as confidential any scientific, preclinical, clinical, or formulation data and information that the sponsor of the parent clinical trial deems to be proprietary and confidential.

IRB approval of the informed consent form(s) is not required at the time of submission of the application. However, drafts of informed consent form(s) for the parent clinical trial and the mechanistic studies, if different, must be included as part of Appendix A. While drafts of the parent clinical trial consent forms at all participating sites are not required, it would be useful to include them if they are available. It is recommended that applications submitted under this program have clear language in the informed consent form(s) that distinguishes mechanistic studies from the clinical trials with which they are linked. It is also recommended that the following items be clarified: (1) additional blood or tissue that will be collected as part of the mechanistic study; (2) the right of the subjects to refuse to participate in the mechanistic study and still participate in the clinical trial; and (3) no charges to the subject for participation in the mechanistic studies. Any incentives provided to subjects to participate in the mechanistic studies (if in addition to those under the parent trial) should be clearly described and strongly justified.

In order to ensure coordination between the mechanistic studies and the parent clinical trial, the clinical trial principal investigator and his or her academic institution, the sponsor of the parent clinical trial (including drug companies, if applicable), and the holder of the IND, if not one of the above, must provide written agreement for the conduct of the mechanistic studies as presented in the application.

Prior to award, the applicant must provide to the funding institute a memorandum of understanding signed by the applicant, an appropriate representative of the applicant institution, the principal investigator of the parent clinical trial and his or her academic institution, an appropriate representative of the sponsor of the parent clinical trial and holder of the IND, if applicable and not one of the above.

This memorandum will confirm agreement among the various parties and will outline the terms and conditions of the agreement in the following areas: 1) ownership, analysis, access, and release of data from the mechanistic studies; 2) access to the data from the parent clinical trial (how/when) that is needed to analyze the mechanistic studies, including procedures for prevention of unblinding of the parent trial; 3) documentation of quality assurance procedures for both the parent clinical trial and the mechanistic studies, and documentation of Data and Safety Monitoring procedures for the parent clinical trial, especially for efficacy trials; 4) ownership of intellectual property developed by the mechanistic studies; and 5) publication of the mechanistic study results.

When clinical studies or trials are a component of the research proposed, NIAID policy requires that studies be monitored commensurate with the degree of potential risk to study subjects and the complexity of the study. AN UPDATED NIAID policy was published in the NIH Guide on July 8, 2002 and is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-AI-02-032.html. The full policy, including terms and conditions of award, is available at: http://www.niaid.nih.gov/ncn/pdf/clinterm.pdf.

Applicants are encouraged to contact NIAID program staff well in advance of the application submission date to discuss the proposed research program. This will allow staff to assess responsiveness to this RFA and to provide appropriate guidance as needed with regard to this initiative. Discussion with program staff does not guarantee funding of an application.

Specific Instructions for Modular Grant applications. Applications requesting up to $250,000 per year in direct costs must be submitted in a modular budget format. The modular budget format simplifies the preparation of the budget in these applications by limiting the level of budgetary detail. Applicants request direct costs in $25,000 modules. Section C of the research grant application instructions for the PHS 398 at http://grants.nih.gov/grants/funding/phs398/phs398.html includes step-by-step guidance for preparing modular budgets. Applicants must use the currently approved version of the PHS 398. Additional information on modular budgets is available at http://grants.nih.gov/grants/funding/modular/modular.htm.

Plan for Sharing Research Data

All applicants must include a plan for sharing research data in their application. The data sharing policy is available at http://grants.nih.gov/grants/policy/data_sharing. All investigators responding to this funding opportunity should include a description of how final research data will be shared, or explain why data sharing is not possible.

The reasonableness of the data sharing plan or the rationale for not sharing research data will be assessed by the reviewers. However, reviewers will not factor the proposed data sharing plan into the determination of scientific merit or the priority score.

Sharing Research Resources

NIH policy requires that grant awardee recipients make unique research resources readily available for research purposes to qualified individuals within the scientific community after publication (NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/index.htm and http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part7.htm#_Toc54600131). Investigators responding to this funding opportunity should include a plan for sharing research resources addressing how unique research resources will be shared or explain why sharing is not possible.

The adequacy of the resources sharing plan and any related data sharing plans will be considered by Program staff of the funding organization when making recommendations about funding applications. The effectiveness of the resource sharing will be evaluated as part of the administrative review of each non-competing Grant Progress Report (PHS 2590, http://grants.nih.gov/grants/funding/2590/2590.htm). See Section VI.3. Reporting.

Section V. Application Review Information

1. Criteria

Only the review criteria described below will be considered in the review process.

The following will be considered in making funding decisions:

- Scientific merit of the proposed project as determined by peer review
- Availability of funds
- Relevance of program priorities

2. Review and Selection Process

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by NIAID in accordance with the review criteria stated below.

As part of the initial merit review, all applications will:

- Undergo a selection process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score.
- Receive a written critique.
- Receive a second level of review by National Advisory Council(s) of the assigned Institute(s).

The goals of NIH supported research are to advance our understanding of biological systems, to improve the control of disease, and to enhance health. In their written critiques, reviewers will be asked to comment on each of the following criteria in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that an application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge or clinical practice be advanced? What will be the effect of these studies on the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Approach: Are the conceptual or clinical framework, design, methods, and analyses adequately developed, well integrated, well reasoned, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

Innovation: Is the project original and innovative? For example: Does the project challenge existing paradigms or clinical practice; address an innovative hypothesis or critical barrier to progress in the field? Does the project develop or employ novel concepts, approaches, methodologies, tools, or technologies for this area?

Investigators: Are the investigators appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers?

Does the investigative team bring complementary and integrated expertise to the project (if applicable)?

Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed studies benefit from unique features of the scientific environment, or subject populations, or employ useful collaborative arrangements? Is there evidence of institutional support?

2.A. Additional Review Criteria:

In addition to the above criteria, the following items will continue to be considered in the determination of scientific merit and the priority score:

Protection of Human Subjects from Research Risk: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed (see the Research Plan, Section E on Human Subjects in the PHS Form 398).

Inclusion of Women, Minorities and Children in Research: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research will be assessed. Plans for the recruitment and retention of subjects will also be evaluated (see the Research Plan, Section E on Human Subjects in the PHS Form 398).

Care and Use of Vertebrate Animals in Research: If vertebrate animals are to be used in the project, the five items described under Section F of the PHS Form 398 research grant application instructions will be assessed.

Biohazards: If materials or procedures are proposed that are potentially hazardous to research personnel and/or the environment, determine if the proposed protection is adequate.

2.B. Additional Review Considerations

Budget: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research. The priority score should not be affected by the evaluation of the budget.

2.C. Sharing Research Data

Data Sharing Plan: The reasonableness of the data sharing plan or the rationale for not sharing research data may be assessed by the reviewers. However, reviewers will not factor the proposed data sharing plan into the determination of scientific merit or the priority score. The funding organization will be responsible for monitoring the data sharing policy. http://grants.nih.gov/grants/policy/data_sharing.

Program staff will be responsible for the administrative review of the plan for sharing research resources.

The adequacy of the resources sharing plan will be considered by Program staff of the funding organization when making recommendations about funding applications. Program staff may negotiate modifications of the data and resource sharing plans with the awardee before recommending funding of an application. The final version of the data and resource sharing plans negotiated by both will become a condition of the award of the grant. The effectiveness of the resource sharing will be evaluated as part of the administrative review of each non-competing Grant Progress Report (PHS 2590). See Section VI.3. Reporting.

3. Anticipated Announcement and Award Dates

Not applicable

Section VI. Award Administration Information

1. Award Notices

After the peer review of the application is completed, the Principal Investigator will also receive a written critique called a Summary Statement.

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant. For details, applicants may refer to the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part4.htm).

A formal notification in the form of a Notice of Award (NoA) will be provided to the applicant organization. The NoA signed by the grants management officer is the authorizing document. Once all administrative and programmatic issues have been resolved, the NoA will be generated via email notification from the awarding component to the grantee business official (designated in item 14 on the Application Face Page). If a grantee is not email enabled, a hard copy of the NoA will be mailed to the business official.

Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NoA are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs. See Also Section IV.5. Funding Restrictions.

2. Administrative and National Policy Requirements

All NIH grant and cooperative agreement awards include the NIH Grants Policy Statement as part of the notice of grant award. For these terms of award, see the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part4.htm) and Part II Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part9.htm).

3. Reporting

To assist in the overall evaluation of the research program, the Principal Investigators of grants funded under this RFA will be asked to provide a brief (one to two pages) summary report one year following the end of the project period. The reports will summarize the major scientific knowledge gained and identify other substantive outcomes such as publications, patents, and new grants, contracts, or research studies based on the work supported under this RFA.

Awardees will be required to submit the PHS Non-Competing Grant Progress Report, Form 2590 annually (http://grants.nih.gov/grants/funding/2590/2590.htm) and financial statements as required in the NIH Grants Policy Statement.

Section VII. Agency Contacts

We encourage your inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

1. Scientific / Research Contacts:

Annette L. Rothermel, Ph.D.
Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases
Room 3020, MSC-6601
6610 Rockledge Drive
Bethesda, MD 20892-6601
Phone: (301) 496-7104
FAX: (301) 480-1450
Email: arothermel@niaid.nih.gov

Beena Akolkar, Ph.D.
Division of Diabetes, Endocrinology, and Metabolic Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
Room 681, MSC-5460
6707 Democracy Boulevard
Bethesda, MD 20892-5460
Phone: 301-594-8812
FAX: 301-480-3503
Email: akolkarb@niddk.nih.gov

Ursula Utz, Ph.D.
Neural Environment Program
National Institute of Neurological Disorders and Stroke
Room 234, MSC-2134
6001 Executive Boulevard
Bethesda, MD 20892-2134
Phone: 301-496-1431
FAX: 301-480-2424
Email: utzu@mail.nih.gov

Susana A. Serrate-Sztein, M.D.
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Extramural Program
Rheumatic Diseases Branch Chief
6701 Democracy Boulevard, Suite 800, MSC 4872
Bethesda, MD 20892-4872
Telephone: (301)594-5032
FAX: 301-480-4543
Email: szteins@mail.nih.gov

2. Peer Review Contacts:

Mercy Prabhudas, Ph.D.
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases
Room 3256, MSC-7616
6700B Rockledge Drive
Bethesda, MD 20892-7616 (U.S. Postal Service Express or regular mail)
Bethesda, MD 20892 (for express/courier service; non-USPS service)
Phone: 301-451-2615

FAX: 301-402-2638
E-mail: mprabhudas@niaid.nih.gov

3. Financial or Grants Management Contacts:

Ann Devine
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases
Room 2114, MSC-7614
6700B Rockledge Drive
Bethesda, MD 20892-7614
Phone: (301) 402-5601
FAX: (301) 480-3780
Email: adevine@mail.nih.gov

Section VIII. Other Information

Required Federal Citations

Use of Animals in Research:
Recipients of PHS support for activities involving live, vertebrate animals must comply with PHS Policy on Humane Care and Use of Laboratory Animals (http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf) as mandated by the Health Research Extension Act of 1985 (http://grants.nih.gov/grants/olaw/references/hrea1985.htm), and the USDA Animal Welfare Regulations (http://www.nal.usda.gov/awic/legislat/usdaleg1.htm) as applicable.

Human Subjects Protection:
Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm).

Data and Safety Monitoring Plan:
Data and safety monitoring is required for all types of clinical trials, including physiologic toxicity and dose-finding studies (phase I); efficacy studies (Phase II); efficacy, effectiveness and comparative trials (Phase III). Monitoring should be commensurate with risk. The establishment of data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risks to the participants (NIH Policy for Data and Safety Monitoring, NIH Guide for Grants and Contracts, http://grants.nih.gov/grants/guide/notice-files/not98-084.html).

Sharing Research Data:
Investigators submitting an NIH application seeking $500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why this is not possible (http://grants.nih.gov/grants/policy/data_sharing).

Investigators should seek guidance from their institutions, on issues related to institutional policies and local IRB rules, as well as local, State and Federal laws and regulations, including the Privacy Rule. Reviewers will consider the data sharing plan but will not factor the plan into the determination of the scientific merit or the priority score.

NIH Public Access Policy:
NIH-funded investigators are requested to submit to the NIH manuscript submission (NIHMS) system (http://www.nihms.nih.gov) at PubMed Central (PMC) an electronic version of the author's final manuscript upon acceptance for publication, resulting from research supported in whole or in part with

direct costs from NIH. The author's final manuscript is defined as the final version accepted for journal publication, and includes all modifications from the publishing peer review process.

NIH is requesting that authors submit manuscripts resulting from 1) currently funded NIH research projects or 2) previously supported NIH research projects if they are accepted for publication on or after May 2, 2005. The NIH Public Access Policy applies to all research grant and career development award mechanisms, cooperative agreements, contracts, Institutional and Individual Ruth L. Kirschstein National Research Service Awards, as well as NIH intramural research studies. The Policy applies to peer-reviewed, original research publications that have been supported in whole or in part with direct costs from NIH, but it does not apply to book chapters, editorials, reviews, or conference proceedings. Publications resulting from non-NIH-supported research projects should not be submitted.

For more information about the Policy or the submission process please visit the NIH Public Access Policy Web site at http://www.nih.gov/about/publicaccess/ and view the Policy or other Resources and Tools including the Authors' Manual (http://www.nih.gov/about/publicaccess/publicaccess_Manual.htm).

Sharing of Model Organisms:
NIH is committed to support efforts that encourage sharing of important research resources including the sharing of model organisms for biomedical research (see http://grants.nih.gov/grants/policy/model_organism/index.htm). At the same time the NIH recognizes the rights of grantees and contractors to elect and retain title to subject inventions developed with Federal funding pursuant to the Bayh Dole Act (see the NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/index.htm). All investigators submitting an NIH application or contract proposal, beginning with the October 1, 2004 receipt date, are expected to include in the application/proposal a description of a specific plan for sharing and distributing unique model organism research resources generated using NIH funding or state why such sharing is restricted or not possible. This will permit other researchers to benefit from the resources developed with public funding. The inclusion of a model organism sharing plan is not subject to a cost threshold in any year and is expected to be included in all applications where the development of model organisms is anticipated.

Inclusion of Women And Minorities in Clinical Research:
It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43). All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html); a complete copy of the updated Guidelines is available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

Inclusion of Children as Participants in Clinical Research:
The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects (http://grants.nih.gov/grants/funding/children/children.htm).

Required Education on the Protection of Human Subject Participants:
NIH policy requires education on the protection of human subject participants for all investigators submitting NIH applications for research involving human subjects and individuals designated as key personnel. The policy is available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

Human Embryonic Stem Cells (hESC):
Criteria for federal funding of research on hESCs can be found at http://stemcells.nih.gov/index.asp and at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (http://escr.nih.gov). It is the responsibility of the applicant to provide in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s)to be used in the proposed research. Applications that do not provide this information will be returned without review.

Access to Research Data through the Freedom of Information Act:
The Office of Management and Budget (OMB) Circular A-110 has been revised to provide access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm. Applicants may wish to place data collected under this funding opportunity in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

Standards for Privacy of Individually Identifiable Health Information:
The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information", the "Privacy Rule", on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (http://www.hhs.gov/ocr/) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html.

URLs in NIH Grant Applications or Appendices:
All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

Healthy People 2010:
The Public Health Service (PHS) is committed to achieving the health promotion and disease

prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This PA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople.

Authority and Regulations:
This program is described in the Catalog of Federal Domestic Assistance at http://www.cfda.gov/ in the following citations: No. 93.855, Immunology, Allergy, and Transplantation Research, No. 93.847, Diabetes, Endocrinology and Metabolism Research, and No. 93.853, Extramural Research Programs in the Neurosciences and Neurological Diseases, and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Loan Repayment Programs:
NIH encourages applications for educational loan repayment from qualified health professionals who have made a commitment to pursue a research career involving clinical, pediatric, contraception, infertility, and health disparities related areas. The LRP is an important component of NIH's efforts to recruit and retain the next generation of researchers by providing the means for developing a research career unfettered by the burden of student loan debt. Note that an NIH grant is not required for eligibility and concurrent career award and LRP applications are encouraged. The periods of career award and LRP award may overlap providing the LRP recipient with the required commitment of time and effort, as LRP awardees must commit at least 50% of their time (at least 20 hours per week based on a 40 hour week) for two years to the research. For further information, please see: http://www.lrp.nih.gov.

Weekly TOC for this Announcement
NIH Funding Opportunities and Notices

Department of Health and Human Services

National Institutes of Health (NIH)
9000 Rockville Pike
Bethesda, Maryland 20892